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Pregnancy Disease of Sheep

By

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Pregnancy Disease of Sheep

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INTRODUCTION

CLINICAL observation has been the method more frequently employed in the study of pregnancy disease of sheep and far too little has been done in the way of laboratory investigation. It was felt that our theories on the physiology and pathology deserved further work, for numerous contributions to the clinical features of the problem have appeared in our literature. It seems that many half-truths concerning this disease have secured credence, yet it is not that so many of the deductions have been inaccurate, but rather that certain features have been unduly emphasized, or rather that too much was attributed to part of the problem. This study and investigation was started therefore, in order that some of the underlying factors concerned in this disease might be studied and evaluated and some contribution made thereby to our knowledge of the problem. It was not expected that any noteworthy improvements would be made in the available methods for control, altho they might appear more logical, if we could secure a better understanding of the origin and course of the disease. Neither does it appear necessary to review all the literature on the subject, except to point out certain features that may appropriately receive especial attention.

The name "Pregnancy Disease of Sheep" has been adopted for the title of this paper. With no other animal disease, do we seem to have acquired such a profuse synonomy of nomenclature. Platt (1), who made a creditable study of the literature on the subject, lists no less than 19 names and synonyms for this disease. Obviously, some of these names are primarily descriptions intended to designate this characteristic disease of sheep as a specific entity.

It appears that this disease is primarily a toxemia of pregnancy which is very similar in much of its manifestations to the human condition. That terminology alone would be quite appropriate, and yet, because toxemias of pregnancy in our livestock are rather sharply limited to sheep, the more specific designation has been adopted as the title for this bulletin. Some of the names signify an analogy with milk fever of cows, which is an entirely different condition. The term paralysis is often used, and yet that seems

inappropriate, for the mild cases do not become paralyzed and the terminal paralysis of coma is scarcely a justifiable designation for the disease.

It is doubtful indeed if this condition in ewes is in reality a new disease, yet the description of Gilbruth (2) which followed some earlier observations, seems to be one of the first discussions on the problem. It is significant that many of those original observations have been more than justified. Much that was written on the predisposing factors and means of prevention is still appropriate.

The occurrence of the disease seems to be world wide wherever sheep are raised. It is no doubt one of the more serious problems involving the loss of mature sheep in this country. The disease has been more or less familiar in a clinical way in North Dakota for years, altho the recent remarkable growth in our sheep population has brought it to our attention more frequently than formerly. Undoubtedly, many of these owners of new flocks have had little experience in the care and management of sheep, and this may be a contributing factor to its increased frequency. It seems to involve sheep irrespective of breed. Marsh (3) comments on the infrequency under range conditions and its prevalence in farm flocks. Some observers believe it more common in the western or Montana ewes, which have been secured by our North Dakota farmers, than in the native stock. If that is correct, it may suggest that the Montana white face ewes, which are accustomed to abundant exercise, endure confinement in the yards less easily than the natives. We have found it repeatedly in grade and pure bred mutton type sheep, as well as in "western" ewes. The predisposing factors are probably of more significance than the breed. Marsh (3) and Foust (4) concluded that the disease is essentially a disease of aged ewes. It is apparently a disease of mature ewes for we have seen few cases in yearling ewes and yet few of our cases have been old decrepit specimens with broken mouths. We saw on one occasion approximately 75 cases in a flock of ewes which were 4 and 5 years old.

SYMPTOMATOLOGY

This clinical entity has been more or less familiar to veterinarians for years. The symptoms have been repeated by so many writers that it is almost superfluous to enumerate them, except to analyze some of the more striking aspects of the problem. The occurrence alone of several losses in a flock of ewes in advanced pregnancy is a sufficient basis for suspecting the disease. It is by far the most common cause of serious losses among breeding ewes during the winter and early spring in our territory. How much of the loss from so-called "grub in the head" during the winter and early spring has, in reality, been pregnancy disease is difficult to ascertain. The grinding of the teeth is almost a constant symp-

tom. The letters of the owners often convey the information that the sheep are apparently blind, for the mental aberration and visual disturbance or amaurosis are apparent to even a casual observer. They often lie on the sternum with the head turned around to the side.

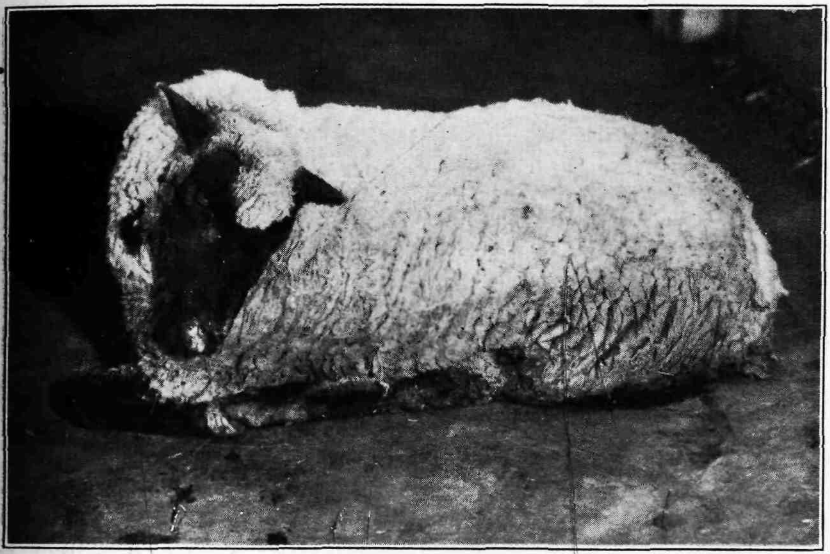


Figure 1. A TYPICAL CASE OF PREGNANCY DISEASE

The temperature possesses little diagnostic significance for it is variable in sheep at best. The labored breathing, which is quite a common symptom, is an attempt on the part of the sheep to compensate for the acidosis. The invasion of the blood by the ketone acids, which decompose the bicarbonate, is followed by an acceleration of respiration to increase ventilation and to remove the carbonic acid. The respiration is sometimes so rapid that it cannot be counted. Rapid emaciation follows the loss of appetite for with the utilization of fat as a consequence of the diminished body carbohydrate, the acidosis is increased. Starvation, therefore, either from lack of feed or from failure to eat complicates the problem. The incoordination, which appears so early in the course of the malady, is an unfailing symptom of the disease.

The observations on morbidity at this laboratory agree with those of other workers. The epizootic proportions might lead one erroneously to assume the possibility of an infectious disease. Losses of from 1 to 25 percent of a flock of ewes are not uncommon, while the case mortality is approximately 90 percent. Death occurs in from 1 to 6 days so that the prognosis is very unfavorable to say the least.

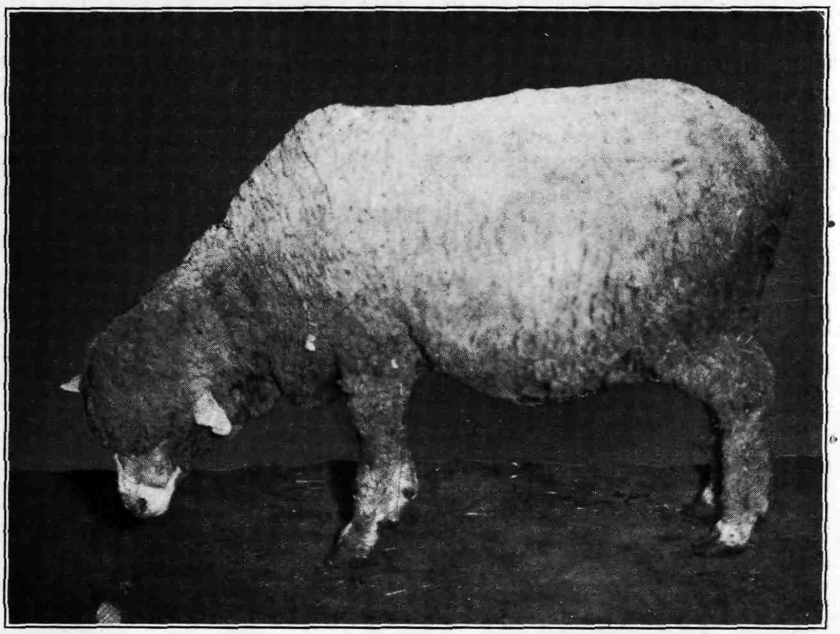


Figure 2. THE EARLY STAGE OF THE TOXEMIA

ETIOLOGY

It seems that this disease in sheep develops and occurs primarily as a toxemia of pregnancy. It has been designated as an autointoxication, but the failure to find a consistent nitrogenous retention in the blood in the disease does not lend support to that assumption. It is generally recognized as a complication of advanced pregnancy, altho few comparisons have been made between the disease in sheep and the human toxemias of pregnancy. The alterations in pregnancy disease of sheep seem to be parallel to much of the functional and morphological pathology of the disease in the human. This work shows a remarkable similarity with but a few minor differences which may easily arise in the generic difference. The cause of these toxemias, to quote Stander (6) is probably an extra demand on the organs of elimination and the failure of those organs to keep pace with the excretory demand.

Human Toxemias of Pregnancy. These disturbances occur during the latter part of the gestation period at a time of rapid fetal growth which requires an increased quantity of glucose to maintain it. According to Wells (5), the excessive products of metabolism which are thrown into the blood of the mother, both from the fetus and from her own overactive tissues, cause injury to the kidneys leading to further retention and with the sluggish elimination, the liver is injured. This sets up a vicious cycle which leads to an overwhelming of the maternal system with toxic

products derived from her own tissues and those of the fetus. The rapid improvement that often follows the removal of the contents of the uterus almost compels us to concede that the causative agent is produced by the fetus or the placenta.

Stander (6) writes that liver damage is one of the most constant findings in human eclampsia which involves a peripheral necrosis of the liver lobule. Acidosis is another fundamental finding which involves ketosis and increased urinary ammonia. The kidney injury involves a nephrosis, albuminuria and edema. There is an increase in the uric and lactic acids of the blood and a decreased CO_2 combining power. There is hypertension, visual disturbance, amaurosis and the eclamptic convulsions, all of which are equally applicable to the disease in sheep except the edema and the increase in uric and lactic acids, while we have no simple easy way of ascertaining blood pressure in sheep. While tetany in the eclamptic sense is by no means typical of the disease in sheep, the toxic symptoms at least are striking in their similarity.

The human lesions, like in sheep, involve the liver and kidney. Bell (7) states that the lesions of the disease are more severe in the liver than in the kidney, where there is an abundant accumulation of lipoid droplets in the cells of the convoluted tubules. The liver shows necrosis, cloudy swelling and fatty metamorphosis. MacCallum (8) and LeDoux (9) both state that the characteristic liver pathology involves a peripheral necrosis that is nearer to the portal than to the central vein. That suggests that the injury is from toxic by-products which are carried by the portal and systemic circulations. Most writers frankly admit that the ultimate causation of the human toxemias of pregnancy is still a mystery and that eclampsia is a disease of theories.

PREDISPOSING CAUSES

The correlation of the occurrence of this disease in the sheep with multiparous pregnancies is significant. Numerous writers have noted this fact. It is a commonly reported observation of farmers and veterinarians. We have recorded observations on 53 of our cases in which 43 carried twin lambs, 5 had triplets, and but 5 had single lambs. It may be assumed that a ewe, which is carrying twin lambs, has an increased excretory burden to carry over those with single lambs. This is reflected in the added burden on the kidneys and the detoxicating function of the liver. If a larger proportion of the ewes with multiple pregnancies are victims of this disease, it would seem that there is some objection to the practice of "flushing" the ewes in the fall. This assumes that it is definitely proven that the condition of the ewe governs the number of lambs which are conceived. It may well be assumed that there are toxic by-products of the fetus, which are discharged into the maternal system, and which our analytical methods do not determine. The disease in our experience is only associated with the gravid ewe, which lends further support that this is primarily a

toxemia of pregnancy. It is doubtful indeed, if it occurs in sheep at any other time, altho some workers have assumed that it may so occur. We have repeatedly found in flocks where the disease has developed, that the non-pregnant ewes, yearlings and rams of the flock, which have the same feed, care and management as the pregnant ewes, have remained normal.

Foust,* working at this laboratory, encountered losses among lambs, which were receiving heavy rations of grain, which presented pathological alterations in the liver which were similar to those of pregnancy disease. The symptomatology of "overeating" in feeder lambs, however, in many respects, is unlike this disease. Newsom,* who has studied that problem in Colorado, does not believe that the two conditions are identical.

The examination of the livers from 11 sheep, which were sick or had died from the overeating of grain, revealed only two with any undue fatty infiltration while 9 appeared quite normal. The two did not approach the serious retrograde fatty changes which are pathognomonic for pregnancy disease. Moreover, the kidneys of those sheep failed to show any of the fatty changes which are so characteristic of the disease in ewes.

Two references (10, 11) suggest that rams and non-pregnant ewes may likewise be affected with the disease. Bruce (11), however, in his article mentioned that while the stercoremia occurred in the males and non-pregnant females, it was more serious in the pregnant ewes. Digestive disturbances were present in a large part of the flock. It is the general impression, nevertheless, that the non-pregnant animals would no doubt survive under the same conditions in general under which the ewes, which die, are fed and handled.

It seems plausible that sheep may have a low factor of safety in their bodily makeup and that may readily explain the frequency of the disease, while toxemias of pregnancy are rare or unknown in horses, cattle, and hogs. A corollary of this syndrome is the common observation, "that a sick sheep seldom recovers." This may explain the occasional case, which we encounter in flocks, which have adequate exercise and an ideal ration. Those individuals therefore, which succumb, may have a low reserve, for the overloaded maternal mechanism cannot support itself and the developing lambs.

There seems to be no record of the occurrence of the disease after parturition. This is further support of the theory that it is a pregnancy toxemia. This assumes that the lambing sickness of Grieg (12) is an entirely different entity and which is comparable to milk fever of cattle in its altered physiology. Several writers including Dill (13) Dimock and his associates (14), and Bruce (11)

*Dr. H. L. Foust, personal communication.
*Dr. L. E. Newsom, Colorado Agricultural College, personal communication.

have commented on the fact that ewes recover when parturition occurs shortly after the onset of the symptoms. The explanation of this phenomena would assume that the liver of such ewes is not irreparably damaged, so that with the evacuation of the uterus there is an immediate reduction in the detoxicating and excretory burden of the ewe's metabolism. Dimock (14) likewise mentions that the lambs are found alive in the advanced stages of the disease. It is not uncommon to have them expelled alive. This agrees with our experience altho the lambs in such flocks are often weak, but this is likewise referable to the conditions of feed and exercise. The following data illustrates the beneficial effects which may result in a case when parturition occurs.

L. N. 26038. This ewe was decidedly unsteady on her feet when she arrived for she was barely able to stand. The symptoms were first observed on the previous evening.

The urine examinations showed a pH of 7.4, acetone 0.15 percent, ammonia 83.2 milligrams percent, blood CO_2, 36.5 vols. percent. Parturition occurred and by the next day, the visible condition of the ewe was greatly improved. The urine then had a pH of 6.4, acetone 0.15 percent, ammonia 67. milligrams percent, and a blood CO_2 of 57.7. A marked improvement was apparent on the second day for the urine then showed a pH of 7.8, acetone .003 percent and only 6.4 milligrams percent of ammonia. Parturition had therefore promptly relieved a maternal mechanism which was fast becoming overloaded.

Clinical observations do not justify the assumption that the disease is infectious in character but rather arises in a profound metabolic disturbance. Glover et al. (15) were inclined to incriminate a specific infection but this does not seem to have been substantiated. The Kentucky workers (14) failed to transmit the disease or to isolate a causative organism. Only a nominal amount of bacteriologic work has been done on the disease, at this laboratory but the results were negative.

EXCITING CAUSES

There is no other feature of the problem which is so badly confused as the causal relationships of the disease. One method of approach, would be to try to reproduce the disease by varying certain factors in the care and management of experimental flocks of sheep. This would no doubt be an expensive procedure and probably no more useful than a careful study of the conditions under which the disease is regularly found. That method has been followed in our work. There has been a tendency on the part of many observers to select certain features that are significant in this disease and attach undue emphasis to those aspects of the problem. A careful study however of the conditions which prevail when the disease develops, indicates that it occurs under two fairly

well defined sets of conditions which seem to react unfavorably on the pregnant ewe.

First. It occurs in flocks, which are in good condition and which are well fed, on a ration which is apparently adequate for their nutritional needs. We usually find however, that when serious losses occur, that a lack of exercise can be incriminated. Alfalfa hay is often available on those farms while grain is often fed in addition. Dr. T. O. Brandenburg of Lakota, North Dakota, has found it frequently in flocks which have had sweet clover hay, yet their exercise had been limited. These sheep are usually in fair to good condition and the normal ewes of the flock produce vigorous lambs. Dimock (18) on the other hand, mentions its rare occurrence when a good legume hay is available.

Very few of the sheep that have come to our attention have been excessively fat. It appears that this danger probably has been over emphasized. The farmer often assumes that such is the case for a heavy fleece may easily conceal a state of emaciation, thereby leading to a faulty deduction. Some writers including Gilbruth (2), Grieg (12), Traum (16) and M'Fadyean (17) mention this aspect of the problem as almost causal in its implications. If sheep have adequate exercise, there is only a nominal danger of pregnancy disease from liberal feeding. Overfeeding alone, in our experience can seldom be incriminated as the causative factor.

Alfalfa and sweet clover hay have a high ash content. It would certainly appear that sheep which receive such forage should have an adequate intake of calcium. The occurrence of the disease therefore among sheep which receive such hay does not support the assumption that this disease is primarily a calcium deficiency disease.

Farmers frequently report losses which are correlated with the occurrence of bad storms and deep snow drifts. Dimock (18) likewise reports losses after a sudden drop in temperature or after a snowstorm. The sheep under such conditions are either shut in or they are unwilling to go any distance. They secure little exercise and moreover ewes which are heavy with lamb are not very agile. Lack of exercise facilitates intestinal stagnation and does not encourage vigorous bodily elimination, either from the lungs or from the bowel tract. A sudden overloading of the detoxicating function of the liver therefore, may explain why these cases suddenly develop in flocks which are in a good state of nutrition.

The loss which occurred in one flock (L. N. 21935), illustrates the ease with which the metabolic balance of these ewes in advanced pregnancy, may be easily upset. A loss of 19 occurred in a flock of 101 Shropshire ewes within a period of about 2 weeks. These ewes were in excellent condition and had been permitted to run in the fields during the open winter. They had received an ample ration of alfalfa hay but with little grain. A blizzard

occurred in early March, when they were shut in the yard, and the losses occurred. The deaths were promptly checked when the ewes were again turned out in the fields. Twins were the rule and all lambs were large and vigorous.

The disease appeared in a band of about 1000 ewes which had been fed on alfalfa and corn fodder during the winter. They were not too fat but had secured rather limited exercise. About 60 ewes developed the disease, within about 6 days after sweet clover straw was substituted for the alfalfa. The 27 rams of the flock remained normal with the same ration. Forced exercise and the resumption of the alfalfa promptly checked the trouble.

Second. It occurs in sheep which have an inadequate ration. This group includes the larger part of our cases and the reports in our correspondence likewise show an insufficient ration in a large part of the flocks. Many of these sheep are actually thin. This applies to the affected individuals as well as to those which are apparently normal. These flocks usually have more opportunity for exercise than does the other group of cases in which the exercise factor is primarily to blame. Alexander (19) mentions its frequency in pregnant ewes that have been underexercised and persistently fed large quantities of bulky coarse, dry roughage, such as timothy hay, swale hay, weathered corn stover, old straw and frosted withered grass. Lytle (20) and Howarth (21) mention that there is a predisposition to the disease from a diet which is rich in proteins, but this does not agree with our observations. Rations of swale hay, corn fodder, and flax straw are not excessively rich in protein to say the least.

We find that the owner has been using straw, corn fodder, pigeon grass, flax straw, wild hay, prairie hay and usually an inadequate grain ration. Some writers comment on the bulkiness of the ration, but it may likewise be mentioned that the nutritional intake is inadequate for the ewe and the developing lambs. It is quite true, that there may be a negative calcium balance with such rations, but the pathology of the cases which develop on such feed is no different than that in sheep which have had ideal rations, except perhaps the presence of emaciation.

Dill (13) proposes a classification of three diseases, while apparently one clinical entity is described, altho he mentions its occurrence under somewhat different conditions. The symptoms, which he describes for blind staggers, preparturient anemia, and pregnancy disease are quite similar. An attempt is made to differentiate pregnancy disease from preparturient anemia and yet the distinction seems to have been made that one condition arises in lack of exercise, while the anemia follows inadequate nutrition. The fact was overlooked, that the pathologic alterations show a remarkable similarity in all of these sheep. The same functional and

structural changes are found in those which are thin and poor from a deficient ration and in those which are in good to excellent condition but which have secured insufficient exercise.

The following data of hematologic work on cases of pregnancy disease fail to show any indication of anemia. These ewes varied in condition from poor to good. Some of them had been fed so that they should have been anemic, if Dill's classification is a logical one.

Table 1. MORPHOLOGY OF THE BLOOD IN PREGNANCY DISEASE

Sheep No.	Erythrocytes per c. mm. of blood in millions	Leucocytes per c. mm. of blood in thousands	Hemoglobin* grams per 100 cc. of blood	Differential leucocytic counts**				
				Poly.	Lymph.	Mono.	Eosin.	Baso.
58	11.3	3.7	4.9	....	....	....	....	....
59	8.9	4.6	7.8	....	....	....	....	....
25860	13.5	....	10.5	62.4	26.4	7.8	2.6	0.4
60	12.3	4.5	4.9	....	....	....	....	....
61	12.3	4.2	9.3	....	....	....	....	....
62	11.2	4.7	8.2	76.0	20.3	3.4	.002	0
64	9.6	4.3	8.5	67.7	27.1	4.5	0.4	0.2
65	11.2	11.2	10.2	78.6	17.8	3.1	0.6	0
439	10.4	8.3	4.5	68.0	26.6	3.4	1.6	0

*The hemoglobin was determined colormetrically by the improved Newcomer method.
**Differential count in percent.

This hematologic work was not extensive but yet it failed to reveal anything significant. The shape, size and the tinctorial properties of the red cells appeared quite normal with nothing suggesting a secondary anemia. Three of the sheep were found to have a low hemoglobin, even tho the number of red cells would have suggested a larger value. These high red cell counts may have arisen from the anhydremia which is a feature of the disease and which has likely concentrated the volume of the blood. Sheep blood is reported by various writers to have from 8 to 12,000,000 erythrocytes and 4 to 12,000 white cells per cubic millimeter.

Br[illegible] (11) applied the term stercoremia to this disease. It is a complication of the nomenclature which implies that autointoxication is primarily involved. We find that the bowel tract usually contains little ingesta for constipation is rarely seen. Indicanuria follows intestinal stagnation, yet the examination of the urine from 37 of these ewes gave a perceptible color with Jaffe's test in but three of the samples. It would seem that intestinal intoxication is not likely more than part of the problem and would not alone be likely to produce the injury in the liver. The failure to find any appreciable retention of nitrogenous metabolites in the blood in this disease, for which the data is included under functional pathology, would further serve to eliminate intestinal stagnation from

the primary role, altho it may well be an accessory factor. Cooke, Rodenbaugh and Whipple (22) report a marked increase in the non-coagulable blood nitrogen in acute intoxication due to intestinal obstruction.

THE CALCIUM ROLE IN PREGNANCY DISEASE

It was logical to assume that calcium metabolism is fundamentally, if not primarily involved in the causation of pregnancy disease. One might conclude that the disease is analagous to milk fever from its occurrence at or about the time of parturition. There is this marked difference, however, that milk fever occurs much less frequently before parturition, while pregnancy disease has not been encountered after that event. It should be emphasized that milk fever is essentially a lesionless disease but not so with pregnancy disease of sheep. The paper of Fish (23) agrees with that of other workers in showing that there is a very significant decrease in the blood calcium and phosphate in milk fever. No work has come to our attention however on the acid-base equilibrium in that disease.

Dimock (18) stated that he and his associates had come to feel that a lowered calcium content of the blood is of real significance as a part of a fundamental change taking place in the body of the pregnant ewe, in predisposing to acidosis or pregnancy disease. They (24) concluded that the calcium content of the blood serum is low in ewes, showing typical symptoms of acidosis of pregnancy and that prevention depends upon maintaining the proper supply of calcium, preferably by the use of feeds relatively high in this element. Grieg (12) however, found the blood calcium values in his cases of pregnancy toxemia to be clearly within the normal range.

Our observations and deductions do not agree with the conclusions of the Kentucky workers. It is doubtful indeed if the metabolism of calcium is primarily involved altho it is pointed out in the discussion on etiology, that this disease is closely linked with the problem of nutrition of the flock. It has moreover, come to our attention repeatedly in flocks, which have had a good legume hay. A personal communication from California (Donald M. Hays) for example, reported heavy losses in ewes which had alfalfa hay with free access to oyster shell flour. Furthermore, the feeding of minerals to livestock has recently been a popular thing, yet five cases developed in a flock of 38 which had access to calcite. Twelve cases, in addition to others which died, came to this laboratory from one flock which had received a widely sold commercial mineral mixture. On the other hand suggestions have been made for the use of mineral supplements, implying that they are beneficial. Mathew (25) for example, reports that South African farmers use bone meal with excellent success as a preventive. The question arises, however, if such observations are adequately controlled.

Hess (26) describes osteomalacia as a complication of human pregnancy, and yet the symptoms in these sheep are those of acid intoxication rather than the convulsive tetany of calcium deficiency. Hastings and Murray (27) found little disturbance in the acid-base equilibrium of parathyroidectomized dogs with a low concentration of calcium. Even if there is a negative calcium balance in some of these ewes, it seems difficult to understand how it can be related to the enormous damage in the liver and to a lesser degree of the kidneys. These lesions are not characteristic of osteomalacia, rickets and tetany which primarily involve abnormalities in calcium and phosphorus metabolism.

The data, which follow, fail to show any significant decrease in the serum calcium of ewes with pregnancy disease, when compared with normal pregnant ewes. Ewes in excellent condition, as well as those which were thin and which had received an inadequate ration, were included in both groups.

Table 2. NORMAL PREGNANT EWES, 1930

Sheep No.	Serum calcium Mgs. Ca. per 100 c.c. blood serum	Mgs. of P. per 100 c.c. of blood: Inorganic blood phosphorus	Mgs. of P. per 100 c.c. of blood: Acid soluble blood phosphorus	Calcium X inorganic phosphorus
229	12.4	5.5	12.6	68.2
105	12.0	4.8	......	57.6
112	12.5	3.0	......	37.5
83	10.7	5.3	9.5	56.7
221	11.5	6.7	12.0	70.0
34	10.6	3.5	9.5	37.1
92	10.6	4.6	10.4	48.8
1273	10.6	4.4	10.0	46.6
197	10.7	5.8	9.3	62.0
173	11.5	5.3	10.3	60.9
175	10.9	4.6	10.1	50.1
207	11.0	4.3	9.6	47.3
200	10.2	3.5	7.6	35.7
21935— 1	9.2	4.3	9.9	39.6
21935— 2	10.1	4.4	10.1	44.4
21935— 3	9.5	3.2	14.2	30.4
22116— 1	9.2	3.1	6.8	28.5
22116— 3	8.8	2.7	6.3	23.8
22119— 1	9.4	4.1	7.8	38.5
22119— 2	9.8	5.4	11.0	53.0
22119— 3	9.8	4.8	8.6	47.0
Average	10.5	4.4	9.8	47.2

Table 3. EWES WITH PREGNANCY DISEASE, 1930

Sheep No.	Serum calcium Mgs. Ca. per 100 c.c. blood serum	Mgs. of P. per 100 c.c. of blood		Calcium X inorganic phosphorus
		Inorganic blood phosphorus	Acid soluble blood phosphorus	
14	9.1	7.4	11.2	67.3
15	8.9	7.0	11.7	62.0
16	8.6	8.0	11.1	68.8
17	9.5	7.7	10.6	73.2
18	9.7	12.1	17.5	117.4
19	12.1	7.6	12.8	92.0
20	8.8	4.7	9.0	41.4
21	8.7	7.3	12.4	63.5
22	8.3	5.0	10.6	41.5
23	7.9	5.2	9.1	41.1
22116	9.2	3.1	8.3	28.5
51	10.1	4.7	10.0	47.5
124	9.4	3.4	6.9	32.0
125	8.7	4.2	8.4	36.5
52	9.2	6.7	12.5	61.6
Average	9.2	6.3	10.8	58.3

Table 4. EWES WITH PREGNANCY DISEASE, 1931
Serum calcium

Sheep No.	Mgs. Ca. per 100 c.c. blood serum	Sheep No.	Mgs. Ca. per 100 c.c. blood serum	Sheep No.	Mgs. Ca. per 100 c.c. blood serum
24071	10.0	60	9.9	67	10.4
58	10.3	24190	11.2	68	10.8
59	10.5	63	14.6	69	11.0
62	6.9	64	13.2	70	10.6
61	11.0	65	11.4	71	11.9
24119	9.9	66	12.5	72	10.5
		Average 11.0 mgs.			

The method of Fiske and Subbarrow (28) was used for the determination of blood phosphorus. The method of Clark and Collip (29) was used for the determination of the serum calcium in 1930, while the method of Roe and Kahn (30) was used in 1931.

Fish (23) points out the significance of a uniformly low product of the blood calcium and inorganic phosphorus. He reports products of 50.0 for normal milking cows and 8.1 as the average for the milk fever cases. We did not find a parallel condition in our cases of pregnancy disease, for the average of 47.2 for the normal ewes was less than 58.3 for the clinical cases of the disease. Platt (1) in an analysis of the calcium theory found little to support it. He failed to reproduce the disease in an experiment with heavy feeding and lack of exercise or with a low calcium ration.

The Relation of the Acidosis to the Calcium Theory. The Kentucky workers have evidently assumed that the acidosis of pregnancy disease is related to a decreased calcium content of the

blood, for Dimock (18) mentioned that the two important mineral buffers of the blood which may vary in acidosis are calcium and potassium.

Little information can be found to support that statement, for the bicarbonates and phosphates of sodium and potassium are primarily the buffer salts of the blood. Peters and Van Slyke (31) state that one of the early effects of acidosis is to wash out the sodium and to a lesser extent the potassium, calcium and magnesium from the body. It seems therefore, that if there is a decrease in the serum calcium in this disease, which appears doubtful from our studies, it is more likely the result, rather than the cause of the diminished alkaline reserve. The calcium content of the blood therefore can scarcely be taken as a measure of the acid-base balance.

Table 5. EFFECT OF VARIOUS TREATMENTS ON THE CO_2 COMBINING POWER OF THE BLOOD

CO_2 in volumes percent of the blood plasma

Sheep No.	CO_2 value before treatment	Treatment	CO_2 value after treatment	Result
19	26.8	Glucose, sod. bicarbonate	48.2	Destroyed
21	31.9	Glucose, sod. bicarbonate, Mg SO_4	49.0	Died
22	45.0	Glucose, sod. bicarbonate, Mg SO_4	61.4	Died
23960	39.5	Glucose, insulin, sod. bicarbonate	72.0	Died
23962	38.0	Glucose, insulin, sod. bicarbonate	86.2	Died
23969	44.5	Glucose, insulin, sod. bicarbonate	74.8	Died
24071	38.2	Glucose, insulin, sod. bicarbonate	57.8	Recovered
24161	51.2	Sod. bicarbonate	78.8	Recovered
Average	39.4	Average after treatment	66.0	

Table 6. DATA ON EWES WHICH RECEIVED INJECTIONS OF CALCIUM SOLUTIONS INTRAVENOUSLY

CO_2 in volumes percent of the blood plasma

Sheep No.	Preliminary CO_2 value	Treatment	CO_2 value after treatment	Result
16	40.5	Calcium gluconate	38.5	Died
24139	37.0	50 c.c.—6% Ca-gluconate	36.0 Next day	
	Recovery followed parturition			
24262	41.4	10 c.c.—20% $CaCl_2$ Soln.	41.4	Died
24287	39.0	10 c.c.—20% $CaCl_2$ Soln.	39.0	Died
24371	39.0	$CaCl_2$ Solution	53.2	Recovered
72	48.5	$CaCl_2$ Solution	46.6	Died
74	39.0	Calcium gluconate	20.4	Died
78	40.8	Calcium gluconate	42.7	Died
79	36.0	50 c.c.—4% $CaCl_2$ Soln.	38.1	Died
80	46.5	50 c.c.—4% $CaCl_2$ Soln.	47.1	Died
82	35.1	50 c.c.—6% Ca-gluconate	34.2	Died
434	47.5	50 c.c.—6% Ca-gluconate	32.8	Died
454	42.8	50 c.c.—6% Ca-gluconate	30.0	Died
460	54.1	50 c.c.—6% Ca-gluconate	51.9	Died
Average	41.9	Average	39.4	

The administration therefore, of sodium bicarbonate by way of the mouth, produced quite a marked improvement in the buffering capacity of the blood by the following day. This illustrates the physiological action of the sodium bicarbonate rather than its therapeutic efficiency, for the treatment was seldom successful. The intravenous injection of calcium on the other hand, either in the form of the chloride or of the gluconate, failed to show any such response either immediately or as a residual effect.

THE PATHOLOGY OF THE DISEASE

The gross lesions of the disease are usually limited to the liver and are described in detail under the pathology of that organ. These changes are usually characteristic enough to justify a diagnosis, particularly when the history and symptomalogy are considered. The digestive tract has seldom shown any sign of inflammation. There is usually little fluid or ingesta present, for the loss of appetite is one of the early features of the disease. There is seldom any excessive amount of fecal material in the large bowel. The gross appearance of the kidneys is ordinarily normal with their size and color unaltered, but a further discussion is devoted to their microscopic pathology. The uterus and its contents seldom present any abnormalities altho multiple pregnancies are the rule.

The appearance of the other organs shows nothing unusual. A thoro and careful histologic study of much of our material substantiates the conclusion that the pathology of the disease is confined essentially to the liver and kidneys. The lungs, lymph glands, pancreas, thyroid, and brain seem quite normal. The thyroid contains an abundance of colloid which would suggest a normal physiologic condition, nor has any evidence of hyperplasia been seen. The normal microscopic appearance of the cerebrum and cerebellum indicates that the mental aberration is physiologic and arises from the acid intoxication rather than from any pathologic involvement of the central nervous system itself.

The spleen shows in most cases a rather unusual amount of brown pigment. This is probably referable to the autolytic processes in the liver, for little other evidence of abnormal blood destruction was found. The spleen is otherwise normal.

A thoro study of the heart material has failed to show any significant abnormalities except the frequent presence of Sarcocystis infection. The fat stains did not show the presence of any retrograde changes.

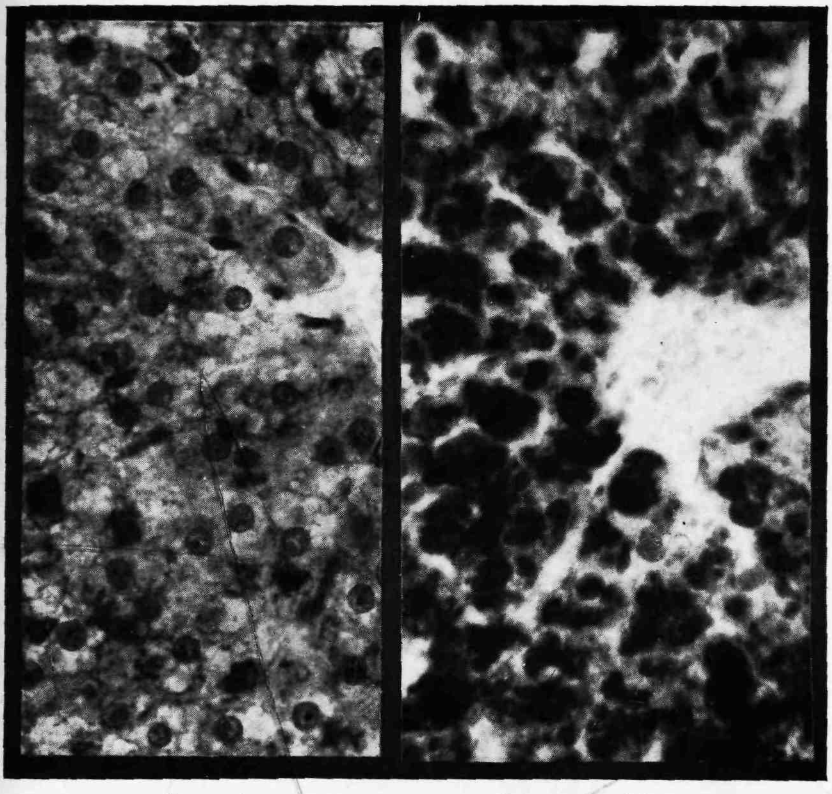
The Liver often presents a striking appearance on necropsy. There is a marked alteration in the color from the reddish brown of a normal animal, so that it assumes a tawny yellow, clay, or putty color. It is very friable and the cooked appearance is evidence of the extreme degree of parenchymatous injury. Hutyra and Marek

(32) describe an acute diffuse parenchymatous hepatitis of sheep which undoubtedly is identical with pregnancy disease, yet the term hepatitis in the sense of an inflammation seems to be scarcely appropriate. It is interesting to note in Hutyra and Marek that Azary in 1883 commented on the resemblance of that condition to the acute yellow atrophy of the liver encountered in human pregnancy.

It is in the liver that we must look for the morphological changes which are responsible for the disturbance in the animal's physiological mechanism and to which the symptoms are due. It must be emphasized, however, that this fatty metamorphosis is the result of injury, rather than an evidence of plethora, altho it has been so assumed. Bell (7) mentions that a fatty liver cannot be produced in starved animals. This might appropriately apply to the so-called anemic cases of Dill. Wells (5) mentions too, that animals starved to an extremely low fat content do not develop the typical fatty liver of phosphorus poisoning. The fatty degeneration of the liver involves an infiltration of neutral fat from the outside into the cells which have degenerated by the action of poisons or other injurious influences. This explains the enormous increase in the lipoidal content in these livers.

The livers of a large number of our cases, about 50 of them, have been examined histologically and a remarkable uniformity in the character of the microscopic changes is seen. The differences are largely a matter of the degree and extent of the injury. The cytoplasm of the cells, rather than the nuclei, is involved. There seems to be little actual necrosis, for the nuclei are ordinarily intact altho pressed to one side of the cell by the fat globules. Vacuolation of the cytoplasm is common, while the cells in many areas have a granular appearance. The use of a fat stain (Oil-Red-O) clearly shows the extensive degree of injury and the enormous extent of the retrograde fatty changes. This condition of the liver in ewes in winter and spring is really pathognomonic for pregnancy disease. It is doubtful if any other disease of livestock involves such an extensive degree of fatty change in the liver A study of the references given under human toxemias of pregnancy reveals that the pathology of that disease shows a remarkable similarity to the changes in the livers in these sheep.

It seems from our studies that the injury, in most cases, develops in the beginning around the periphery of the lobule. M'Fadyean (17) likewise made a similar observation altho it was sometimes more complete in the central zone. This delicate network of fat is even visible in the gross appearance of some of the livers. The following photomicrographs show the contrast between normal liver tissue and that found injured in pregnancy disease.



Normal Pregnancy Disease

Figure 3. PHOTOMICROGRAPHS OF LIVER TISSUE STAINED FOR FAT

Oil Red -O-Stain

This suggests that the toxic and injurious substances are carried by the blood, so that the cells at the outer border of the lobules are therefore the first to be injured. Many of the livers in the advanced stages of the disease show few if any cells which would likely be capable of normal function. Undoubtedly, such livers are no longer capable of an adequate glycogenic function or of performing their normal detoxicating process of oxidation. The liver is one of the main reservoirs of carbohydrate and while quantitative studies have not yet been attempted on the liver glycogen in this condition, it can be seen how the ketosis may follow the injury to the liver. This is discussed in further detail under the functional pathology.

Table 7 shows the striking alteration in cellular composition which occurs in the disease. The analysis of 10 sheep livers for moisture and crude fat were made for us by T. H. Hopper, Agricultural Chemist of the Experiment Station, using the ether extraction method on the ground and dried liver.

Table 7. MOISTURE AND CRUDE FAT CONTENTS OF SHEEP LIVERS
Pregnancy disease compared with normal sheep.

Sheep No.	Condition	Fresh basis			Crude fat (dry basis)
		Moisture	Dry matter	Crude fat	
		%	%	%	%
62	Abnormal	57.94	42.06	25.51	60.65
63	"	51.42	48.52	33.20	68.42
64	"	47.14	52.86	36.10	68.29
65	"	52.83	47.17	29.10	61.69
434	"	67.54	32.46	13.54	41.71
439	"	64.60	35.40	13.18	37.23
1	Normal	70.65	29.35	3.15	10.73
2	"	68.66	31.34	3.27	10.43
3	"	70.21	29.79	3.32	11.14
464	"	72.76	27.24	1.36	4.99

The moisture content of the livers of the ewes with pregnancy disease was notably lower than that of the normal controls. This may have been the result of the process of dehydration, which is a significant feature of the disease, or it may simply mean that a fat tissue contains relatively less moisture than one with a lower fat content.

Microscopic study of these livers with the fat stain revealed a close correlation of their appearance and their content of crude fat. These data give conclusive concrete evidence of the enormous increase in fat which is deposited in the livers of these ewes when compared with the normal sheep livers. Wells (5) mentions in like manner that livers injured with phosphorus may contain 75 percent of the dry weight in fat. It is interesting to note than No. 464 was a pregnant ewe which had presented a mild toxemia about 2 weeks previous to slaughter but which had recovered. The fatty changes were well established in No. 439 around the periphery of the lobules, altho less than half of the area was involved. No. 64, on the other hand, showed an enormously greater amount of fat than No. 439, for most of the cells were red with the fat stain. This extensive degree of injury to the liver will be the limiting feature for any treatment, for the factor of safety has no doubt been exceeded in the injurious process.

The Kidneys in pregnancy disease likewise show a remarkable uniformity in the character of the lesions which are present. Previous comment was made on the lack of gross changes in the kidneys. There seems to be little recognizable change in the glomeruli, but there is apparently some swelling of the epithelium lining the convoluted tubules. Casts have not been encountered in our kidney sections. The most significant finding is the presence of fat droplets in the epithelial cells of the ascending and descending limbs of Henle's loops at the edge of the cortex. More advanced cases show a greater degree of involvement. It is patchy in the beginning and involves groups of tubules. The cytoplasm of the cells is often "muddy" and granular. The loops of Henle seem to be involved in the milder cases while the injury to the convoluted tubules seems to be a subsequent process. No fatty change has

been observed in the glomeruli. This characteristic lesion of the disease has not been observed in normal sheep. No trace of any cellular infiltration has been observed, so it is no doubt a toxic injury rather than one of inflammation.

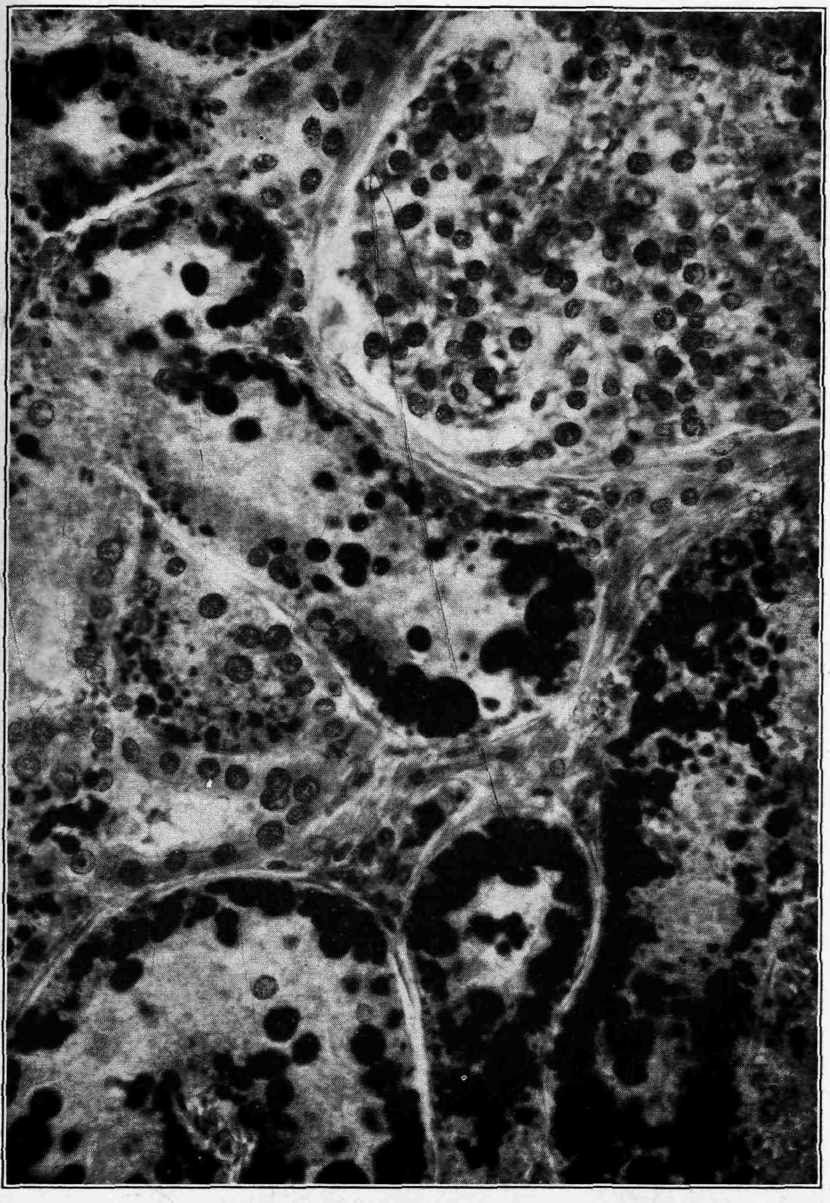


Figure 4. PHOTOMICROGRAPH OF FAT STAIN
Nephrosis of the Kidney in Pregnancy Disease
Oil Red-O-Stain

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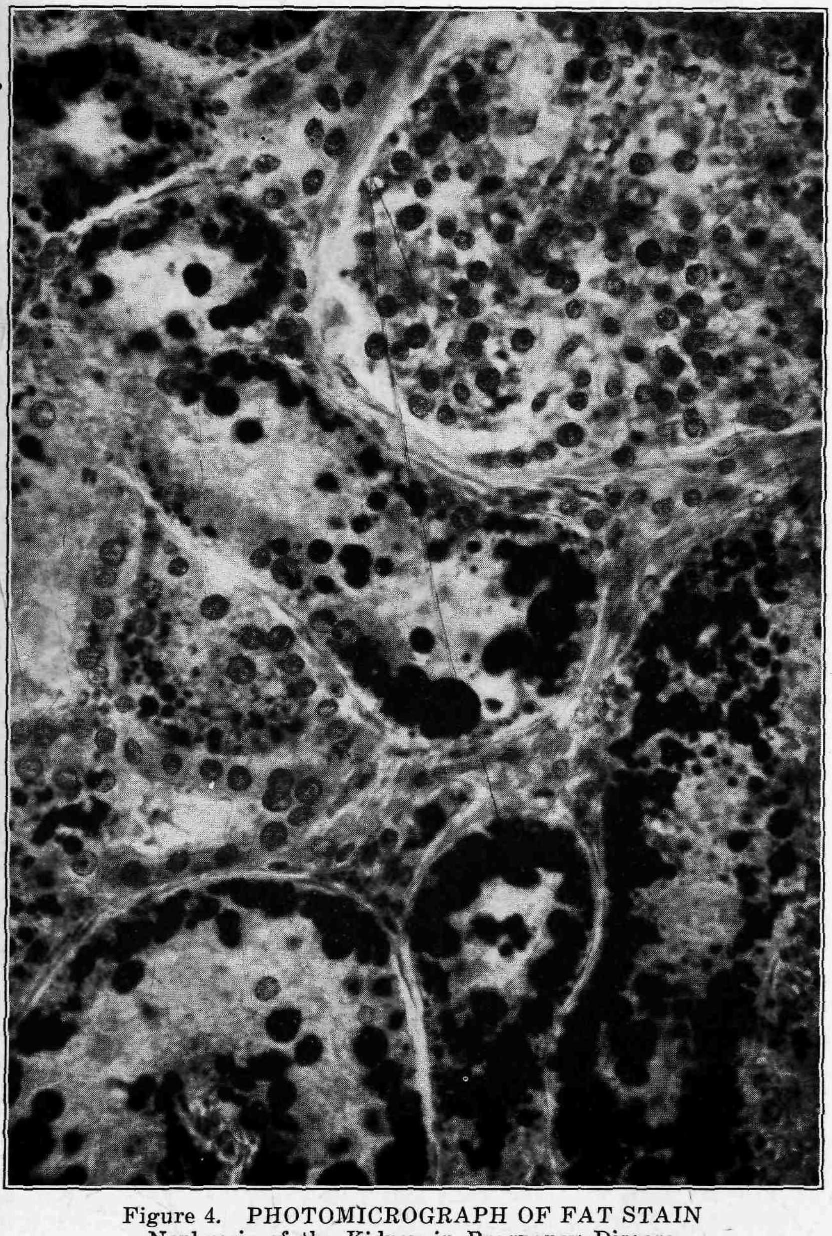

Figure 4. PHOTOMICROGRAPH OF FAT STAIN
Nephrosis of the Kidney in Pregnancy Disease
Oil Red-O-Stain

This type of injury is a nephrosis and is related to the albuminuria, and would not likely terminate fatally in itself. It is noted under the functional pathology that very little nitrogenous retention occurs with this type of kidney injury. This lesion is quite comparable to the changes in the human kidney in toxemias of pregnancy. It probably arises from the excretion of toxic and injurious products of metabolism. The diuresis, which is a feature of the disease, may be partly due to an inability of these injured tubules to concentrate the urine properly. The changes in the kidney are no doubt the result rather than the cause of the disease.

THE FUNCTIONAL PATHOLOGY

This phase of the work was an inquiry into the fundamental metabolic alterations in these sheep and a measure of the organic changes which are a part of the disease.

Liver Function. An indirect measure of the extent of damage to the liver was desired, for that seems to be the primary injury. Icterus is never seen in the tissues and while the extent of liver damage is enormous, one seldom finds an undue amount of biliary pigment in the blood and urine. Some trials were made with the various dye excretion methods but no satisfactory results were secured. Rose bengal and tetrachlorphthalein were used but a satisfactory matching of the dyes with the color in the sheep serum was not obtained.

Blood Sugar. It will be noted in Table 8 that many of the blood sugar values are lower than those for normal ewes. The revised method of Folin (33) was used in this work. A set of 14 control determinations was made on the blood of normal pregnant ewes and an average of 46.1 milligrams percent with a range of 40 to 56.9 milligrams was found. Many values below 30 milligrams were found in the sick ewes. The quantity of blood sugar in some of the samples was too low for even approximate colorimetric comparison. The importance of the relationship of the low blood sugar to the maintenance of the acid base balance is considered under the topic of acetonuria. The glycogen of the liver is one of the main reservoirs of the animal's carbohydrate. It is quite reasonable to conclude, that with such an extent of fatty injury to the liver, the carbohydrate level of the blood will suffer as a consequence and make it impossible for the animal to avoid acidosis. Peters and Van Slyke (31) have compiled information to show that the removal or the severe injury to the liver, as in phosphorus and chloroform injury, is accompanied by a hypoglycemia. It would be expected that the ability of the liver to store glycogen is seriously impaired, and the fasting of these ewes permits the blood sugar to sink to a low level, for the diminished reserve in the liver does not maintain it. A few sugar values in the clinical cases were even higher than in normal sheep (65-75 mgs.). This may be explained on the basis that the carbohydrate intake had not yet diminished

and that the injured liver could not store the excess. The revised Folin method for sugar does not give values as high as the older method. Molasses in the ration has been suggested as a prophylactic treatment but there appears little justification for its use.

On the other hand, the toxemias of human pregnancy do not seem to involve a hypoglycemia according to Peters and Van Slyke (31) and Williams (34). It is possible that the degree of injury in the human liver in that condition is not as severe as in these sheep, for both conditions are correlated with a ketosis, but the factor of starvation is often mentioned for the human which suggests a lack of carbohydrate to say the least.

Table 8. Blood Chemistry
Ewes with pregnancy disease.

Sheep No.	Mgs., per 100 c.c. of blood			Volumes percent of CO_2 per 100 c.c. of blood
	Blood sugar	Non-protein nitrogen	Blood chlorides	
14	25	30	645	36
15	27	35	600	41
16	34	37	555	38.5
17	28	35	580	31.2
18	73	44	565	14.1
19	46	33	580	25.4
20	30	29	575	36.2
21	31	45	600	32.0
22	23	38	575	45
23	65	28	570	42
51	70	25	530	52
124	24	22	575	33
125	54	24	585	40
65	low	29	......	30
66	63	82	......	32
67	24	23	.....	41
68	75	28	.....	39
69	57	34	......	39
70	low	24	......	41
71	56	22	......	54
72	low	33	......	46
73	33	....	......	33
74	low	25	......	39
75	86	62	......	44
78	low	48	......	40
79	low	57	......	36
80	38	23	......	46
82	low	55	......	35

Non-Protein Nitrogen. The method of Koch and McMeekin (35) was used, but very little evidence of the retention of the nitrogenous metabolites was found. Five ewes (Nos. 66, 75, 78, 79 and 82) may be said to have shown some retention. This disease does not involve a uremia for the nephrosis of the kidneys, which is typical of the pregnancy toxemias, is not accompanied by any extreme degree of nitrogenous retention. Previous reference has been made in the discussion of the exciting causes of the disease to the improbability of autointoxication from intestinal obstruction.

Blood Chlorides determined by the method of Short and Gellis (36) showed no significant variations. Five determinations on normal pregnant ewes gave similar values of from 500 to 565 milligrams.

The Acid Base Balance. Dimock and his associates (14) reported that pregnancy disease is undoubtedly an acidosis. They reported finding an acetonuria, an albuminuria, an acid reaction of the urine and a decrease in the buffers of the blood in the disease. This study confirms those findings. The method of Cullen, however, which they used in the examination of the blood of three ewes has found little actual use, for the determination of the carbon dioxide combining capacity of the blood by the well known method of Van Slyke and his associates is the most practical measure of the alkaline reserve of the animal body.

The CO_2 capacity of the blood was determined on 21 apparently normal pregnant ewes and none were found to be less than 50.4 volumes percent; average 54.3. It will be seen from the data in Table 8, that many of the ewes with pregnancy disease show an appreciable decrease in the CO_2 value of the blood. The amounts varied from 14 to 54 volumes percent. Williams (34) reports the blood in human toxemias of pregnancy and eclampsia to vary from 15 to 55 percent. This decrease in the alkaline reserve results from an accumulation of the ketone acids in the blood and tissues, which act like other acids in displacing base from its combination with CO_2. The available alkali for combination with CO_2 is correspondingly diminished.

The Urine in Pregnancy Disease. An albuminuria was found more or less regularly, altho it was inconstant. It is no doubt a result of the nephrosis in the kidneys. The urine of 48 of our cases was examined for albumen which was found in varying amounts in 29 of the specimens but was not detected in 19. Examinations were made for casts in many of the samples but they were not encountered nor have they been seen in the histologic sections of the kidneys.

Changes in the urine are likewise a reflection of the abnormalities in the acid-base balance of the blood. The urine of eight normal pregnant ewes was examined with the Clark and Lubs indicators and the pH found to vary from 8.2 to 8.6, average 8.45. This is in marked contrast to that from ewes with pregnancy disease. Table 9 shows that those urines varied from a pH of 5.2 to 7.4. This is a reflection of the alkali deficit of the blood and of the excretion of diacetic acid and other ketones with a corresponding decrease in the urinary pH. The alkalinity of normal sheep urine arises from the excretion of the mineral bases conjugated with the large amounts of hippuric acid. The substitution of ammonia in combination with the ketone acids for the sodium and potassium ions which are ordinarily excreted, accounts for the abnormality.

Acetonuria seems to be a constant urinary finding. The urine of these ewes has invariably given a positive test for acetone. Lange's modification of the Legal test has been used. Acetone is present in the earliest recognizable stage of the disease so that here is a simple and easy method of confirming the diagnosis. The presence of these acetone bodies in the urine is a reflection of their presence in the blood, tho not necessarily in the same concentration.

The quantitative estimation of acetone in the urine is a simple procedure with the method of Behre (37). It is interesting to note that the urine of 12 normal pregnant ewes in no instance gave a positive qualitative test nor showed more than the barest trace of .001 percent of acetone with Behre's method. The 13 determinations included in Table 9 varied from 0.01 to 0.3 percent of acetone in the urine of these cases of pregnancy disease or as much as 300 times more than with normal ewes. Urine collections for stated intervals were not attempted with these ewes.

Table 9. EXAMINATION OF THE URINE
Ewes with pregnancy disease.

Sheep No.	Acetone percent	pH	Ammonia mgs. per 100 c.c.
49	0.1	....	....
100	0.2	....	....
51	0.075	....	....
53	0.2	6.4	97.
54	0.3	6.6	71.
55	0.1	6.2	24.
25860	.01	5.6	47.
58	....	5.4	130.
59	....	5.2	35.
60	....	6.8	53.
61	....	7.0	210.
25921	.19	7.0	27.
62	.05	6.2	63.
63	.10	6.2	85.
64	.30	6.4	116.
65	.30	6.8	140.
26038	.15	7.4	83.

The presence of acetone bodies in the urine (acetone, beta-hydroxybutyric, and diacetic acids) is the result of insufficient metabolism of carbohydrate, according to Peters and Van Slyke (31). Apparently, an animal body is incapable of carrying the oxidation process of the fats to completion unless a certain amount of carbohydrate is burned simultaneously. Ketosis occurs under three conditions. It may occur (1) in the starving subject, it likewise occurs (2) thru an inability to oxidize carbohydrate (diabetes) and (3) with a deficient endogenous carbohydrate store. Quite likely, therefore, the abnormal organic acid formation arises as the end result of some impairment of the glycogenic function of the badly damaged fatty livers of these sheep. The significance of the low blood sugar is mentioned under that topic. It is doubtful if an increased carbohydrate intake alone would prevent the con-

dition. The damage to the liver from the overwhelming of the detoxicating function by the toxins, precipitates a disturbance in the other functions of the liver, which soon completes the transition to pathology.

The acidosis of human toxemias of pregnancy likewise results in the abnormal formation of unusual amounts of ketones but of lactic and uric acids as well. Here seems to be a difference in the disease, for the following data show no abnormal amounts of either lactic or uric acid in the blood of cases of pregnancy disease, except that several of the sheep (Nos. 72, 73, 75 and 76) had an increased amount of lactic acid. Folin's method (38) was used for uric acid and that of Friedemann and Kendall (39) for lactic acid.

Table 10. Blood, Uric and Lactic Acids
Ewes with pregnancy disease

		Mgs. per 100 c.c. of blood			
Sheep No.	Uric Acid	Lactic Acid	Sheep No.	Uric Acid	Lactic Acid
63	Trace	14.	73	Trace	37.
64	1.3	42.	74	Trace	22.
65	Trace	10.	75	2.8	85.
66	Trace	21.	76	1.6	60.
67	Trace	20.	77	1.7	31.
68	1.6	28.	78	1.4	17.
71	1.4	33.	79	1.7	13.
72	Trace	36.	80	1.6	14.
			82	2.3	13.

The ketone acids rather than uric and lactic acids, seem therefore to be largely responsible for the abnormal amount of organic acid formation in these sheep.

Ammonia. An enormous increase in the urinary ammonia is a characteristic feature of acidosis. It is related to the preservation of the base supply of the body and to the maintenance of an acid-base equilibrium compatible with life. Peters and Van Slyke (31). Urinary ammonia is formed in proportion to the requirements of the body for the excretion of acids (acetone bodies) which could not otherwise be excreted in the urine without undue depletion of the essential alkaline elements. It is characteristic of pregnancy toxemias.

The familiar Permutit method of Folin was used in making the analysis for urinary ammonia. The amounts given in Table 9, which were found in pregnancy disease were in striking contrast with the negligible amounts found in the urine of normal pregnant ewes. The urine of 12 such ewes was examined and the amounts of ammonia present, even in quantities of 5 c.c. of urine, were insufficient for colorimetric determination.

Polyuria. Peters and Van Slyke (31) likewise comment on this significant feature of acidosis. It is a physiological attempt to flush out by dilution, the abnormal amounts of organic acids.

Anhydremia results from the diuresis. Clinical observations on these sheep suggest at least that urinary excretion is greatly increased altho no collections for stated intervals were made. No difficulty was ordinarily encountered in collecting considerable quantities of urine from the sheep, which is in marked contrast to normal ewes. This condition is reflected in the thirst and later in the general lack of fluids in the cadavers.

TREATMENT

Most of the sheep, which we have treated in our work, have died with monotonous regularity, which agrees with the experience of veterinarians that ewes in which this toxemia becomes well established, have invariably died. Dimock (14) reported little success in the treatment of the disease after the appearance of the symptoms. They used magnesium sulfate, calcium lactate, sodium bicarbonate, glucose, and udder inflations. Grieg (12) reports trials with mammary inflation but without any beneficial effect, yet it is promptly effective in lambing sickness.

The writers have been unable as yet to demonstrate any consistent beneficial therapeutic effect from any of the treatments which were tried. Alkaline treatment in the form of intravenous injections of glucose, and sodium bicarbonate per orem and intravenous injections of calcium salts either in the form of the chloride or of the gluconate have been tried repeatedly.

The statement of Baker (40) that calcium gluconate is a specific for this disease does not agree with our experience, nor do any of our veterinarians report such success. No consistent physiologic response has been secured in those sheep which we have treated in an experimental way with calcium gluconate in contrast with the administration of sodium bicarbonate. A comparison of the data in Tables 5 and 6, which shows this failure in physiologic effect on the alkaline reserve, together with its repeated failure in actual therapeutic use does not seem to lend encouragement to the continued use of calcium for pregnancy disease.

The oral administration of 25 grams of sodium bicarbonate twice daily, either alone or combined with the intravenous injection of 50 grams of glucose would seem to be more logical on sheep in the early stage of the disease. Such treatment is worth a trial for it seems to have more technical facts to encourage its use than the injection of calcium gluconate.

An occasional sheep does recover and as such, they represent less toxicity from comparatively less injury to the liver. More satisfaction will be secured by prompt attention to preventive measures directed to the flock itself and those ewes which are still apparently normal, than attempting to treat those which are obviously sick.

PREVENTION

This is primarily a problem of animal husbandry involving adequate rations which of course implies a balanced ration combined with such management as will insure abundant exercise in the ewes. The condition is rare, when the feed, care and management are ideal. The matter of constant exercise must not be disregarded for the pregnant ewe. This is true not only for those which are thin but it is necessary, especially, for the heavy fat ewe with a twin pregnancy. On the other hand, when the ewes are in only fair condition at the beginning of winter, it is desirable to have their condition improving up to parturition.

It will appear from the discussion of the role of calcium in this disease that there is little justification for encouraging the use of calcium or mineral supplements as a means of prevention. Maguire (41) mentions that the use of one-half ounce of mixed minerals daily with a mixture of oats and bran has now eradicated the disease where it formerly prevailed. Comment is made on Mathew's (25) suggestion for the use of bone meal in the discussion on calcium. Citations are made elsewhere in this bulletin on the occurrence of the disease when a mineral supplement was available. It is doubtful if control sheep were fed without the supplement when such success is reported. The writers agree with Dimock (18) that while an adequate intake of calcium is important, that better reliance can be placed on a good legume hay to supply that need, than to feed roughage of inferior quality and to supplement it with a mineral mixture.

The control and prevention of further losses depends on a study of the situation which prevails in the individual flock and making such corrections as appear appropriate. Several writers appear to have considered only one aspect of the problem and to stress the need of reducing the ration to a mere subsistence and compelling the ewes to rustle for their feed. That is quite appropriate for the handling of a flock which is in good condition, for it is primarily a matter of exercise. When it is possible to get the ewes out for some green feed and grass, which is highly digestible, it should be encouraged, if further preventive measures are required. A good pasture is a natural environment for sheep. They automatically secure the needed exercise and the natural succulence of the grass is laxative so that various factors are favorable in preventing further cases of pregnancy disease, when grass is available. When cabbage or roots can be obtained, their use is worth while.

It is advisable to feed the hay at some distance from the shed, so that the ewes will of themselves be compelled to exercise. It is often advisable to drive the flock slowly for a distance of half a mile at least, for experience has shown the beneficial effects of forced exercise. When snow is deep or immediately after a storm, the flock may need especial attention. Various observers report

success in preventing further losses in well fed flocks under such conditions, which agrees with our experience.

Flocks which have had an inadequate nutritional intake are less satisfactory to handle. The ewes are already in advanced pregnancy when losses occur so that insufficient time is available to permit their condition to improve and so avoid a crop of weak lambs, even tho the ewes do survive. The roughage of poor quality should be replaced with a good legume hay together with a sufficient amount of grain or concentrated feed to constitute an adequate ration. The matter of exercise should not be overlooked.

SUMMARY

The term pregnancy disease seems more appropriate than any of the other synonyms which have been used to name this interesting disease of pregnant ewes. The disease is a toxemia of pregnancy, which is quite similar to those conditions in the human, in much of the functional and morphological pathology.

The disease is one of the most common causes of loss among pregnant ewes in the late winter and early spring before the appearance of grass. The losses in individual flocks sometimes are as much as 25 percent, while the case mortality is about 90 percent. The predisposing factor of a multiparous pregnancy was recognized long ago. Most of the cases develop during the last month of pregnancy with the greater proportion within a week or two of parturition. It does not seem to occur after the termination of pregnancy.

The disease develops in ewes under two sets of conditions. It occurs in ewes which are well fed and are in fair to excellent condition but it usually involves a lack of exercise in such cases. On the other hand, the same disease develops in sheep which are thin and which have had an inadequate ration. Many times there is opportunity for ample exercise for such sheep but the bulky, coarse forage of poor quality is insufficient for the needs of the ewe and the developing lambs. The disease is clearly metabolic rather than infectious in character. It develops from an overloaded maternal mechanism and an excessive excretory burden, which overwhelms the detoxicating function of the liver, and when the damage occurs in that organ, the symptoms of intoxication from acidosis cannot be avoided. It is not an autointoxication alone, altho that is no doubt a part of the problem. It does not arise primarily as a manifestation of a mineral deficiency disease, altho sheep which receive a ration of inferior quality are no doubt in a negative balance so far as calcium is concerned. The final explanation of the causation of the disease probably will be a subject of speculation for some time to come.

The pathology of pregnancy disease is confined to the liver and kidneys. There is an enormous increase in the fat in the liver,

so that a content as much as 68 percent (dry basis), when compared with 10 to 11 percent for the normal animal has been found. This undoubtedly represents injury from toxic substances and consequent deposition of fat rather than a manifestation of plethora. The damage in the liver, having exceeded the factor of safety, the prognosis from therapeutic measures is unfavorable indeed. The kidney lesion is that of nephrosis, which is largely a result, rather than the cause of the disease.

The acidosis, which arises in a deficient endogenous supply of carbohydrate, which follows liver injury and the impairment of the glycogenic function, is responsible for the altered physiology and the symptoms of the disease. The ketone acids, which form in that abnormal metabolism, promptly deplete the alkaline reserve thru decomposition of the blood bicarbonate, so that the salts of those organic acids are excreted and the acid-base balance of the body protected.

There seems as yet to be little encouragement in attempting to treat those ewes in which the disease is already well established. More satisfaction will be secured by prompt attention to measures of prevention. Liberal exercise will check the losses in flocks which are in good condition where deaths have occurred thru some irregularity in the care. An adequate ration of good quality combined with liberal exercise will be the best safeguard in preventing losses in breeding ewes.

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